Diagnosis and management of congenital diaphragmatic hernia: a 2023 update from the Canadian Congenital Diaphragmatic Hernia Collaborative

Pramod Puligandla ,[1] Erik Skarsgard,[2] Robert Baird,[2] Elena Guadagno ,[3] Alexandra Dimmer,[1] Olivia Ganescu,[1] Nimrah Abbasi,[4] Gabriel Altit ,[5] Mary Brindle,[6] Sairvan Fernandes,[2] Shyamala Dakshinamurti,[7] Helene Flageole,[8] Audrey Hebert,[9] Richard Keijzer,[10] Martin Offringa ,[11] Dylan Patel ,[1] Greg Ryan,[12] Michael Traynor,[13] Augusto Zani,[14] Priscilla Chiu,[15] The Canadian Congenital Diaphragmatic Hernia Collaborative

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For numbered affiliations see end of article.

Correspondence to
Dr Pramod Puligandla, Pediatric Surgery, McGill University Health Centre, Montreal, QC H4A 3J1, Canada; pramod.puligandla@mcgill.ca

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ABSTRACT

Objective The Canadian Congenital Diaphragmatic Hernia (CDH) Collaborative sought to make its existing clinical practice guideline, published in 2018, into a 'living document'.

Design and main outcome measures Critical appraisal of CDH literature adhering to Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. Evidence accumulated between 1 January 2017 and 30 August 2022 was analysed to inform changes to existing or the development of new CDH care recommendations. Strength of consensus was also determined using a modified Delphi process among national experts in the field.

Results Of the 3868 articles retrieved in our search that covered the 15 areas of CDH care, 459 underwent full-text review. Ultimately, 103 articles were used to inform 20 changes to existing recommendations, which included aspects related to prenatal diagnosis, echocardiographic evaluation, pulmonary hypertension management, surgical readiness criteria, the type of surgical repair and long-term health surveillance. Fifteen new CDH care recommendations were also created using this evidence, with most related to the management of pain and the provision of analgesia and neuromuscular blockade for patients with CDH.

Conclusions The 2023 Canadian CDH Collaborative's clinical practice guideline update provides a management framework for infants and children with CDH based on the best available evidence and expert consensus.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Congenital diaphragmatic hernia (CDH) is a developmental defect that requires intensive cardiorespiratory support in the perioperative period.
⇒ The exemplar anomaly in CDH is pulmonary hypoplasia, which manifests as postnatal pulmonary hypertension of variable severity; however, infants with CDH also experience additional multisystem morbidity.
⇒ Multisystem morbidity extends into childhood and adolescence and necessitates long-term health surveillance.

WHAT THIS STUDY ADDS

⇒ This study builds on existing care recommendations published in 2018 that address all phases of CDH care from prenatal diagnosis, to in-hospital care, to post-discharge health surveillance.
⇒ Twenty existing recommendations have been revised, and another 15 new CDH care recommendations have been developed, especially in the area of pain control and analgesia.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study provides a framework for CDH management that continues to reduce unwanted variability in CDH care as well as improve patient outcomes.
⇒ The updated care recommendations provide a pragmatic approach to CDH care that are applicable to all stakeholders involved in CDH care globally.
⇒ The updated care guidelines still allow for innovation and continued advancement in CDH care.

INTRODUCTION

In 2018, the Canadian Congenital Diaphragmatic Hernia (CDH) Collaborative produced a clinical practice guideline (CPG) for the diagnosis and management of CDH.[1] Leveraging national, interdisciplinary expertise and the best available evidence, this guideline reflected a pragmatic approach to optimal CDH management that sought to minimise variations in care. In order to further increase the guideline's uptake and utilisation, we developed a free smartphone application providing ready access to CDH care recommendations and the evidence that informed them.[2] Knowledge synthesis related to care of CDH has been ongoing since 2018, and an update that assimilates recent best evidence using a rigorous appraisal methodology is timely.

Linked

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The scope of this project involved the appraisal and assimilation of the accumulated, best available evidence since 2017 into the existing CPG. As with the original version, the recommendations encompass all phases of CDH care from prenatal diagnosis to in-hospital management to post-discharge health surveillance. This update represents another collaborative effort among CDH experts and thought leaders across Canada and is relevant not only to users in North America, but around the world.

METHODS

Online supplemental appendix 1 provides a detailed description of the methods used by the CDH Collaborative to update the 2018 guidelines, including: (1) the steering committee and working group composition (2) the literature search conducted from 1 January 2017 to 30 August 2022 (figure 1 and online supplemental materials); (3) the evidence appraisal process using Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology[3] (figure 1 and online supplemental appendix 2); (4) the iterative process of evidence assessment leading to modification of existing recommendations or the creation of new ones; (5) the taxonomy used to assign strength of recommendation (figure 2); (6) the modified Delphi endorsement process which established consensus on new or modified guidelines using predetermined thresholds (figure 3); and (7) the management of competing interests. As with the original version, these recommendations encompass all phases of CDH care from prenatal diagnosis to in-hospital management to post-discharge health surveillance.

The following subject areas informed the literature search. If no new evidence was found to compel a significant change to the 2018 recommendations, that subject area's recommendations are 'unchanged'. Recommendations from 2018 that were modified based on new evidence are designated as 'updated' or 'new' based on degree of novelty. Two new subject areas (*management of gastro-oesophageal reflux*, and *analgesia, sedation and neuromuscular blockade*) have been added to the updated guidelines:

1. Prenatal diagnosis and treatment.
2. Fetal therapy.
3. Ventilation.
4. Fundamentals of haemodynamic support.
5. Role of echocardiography.

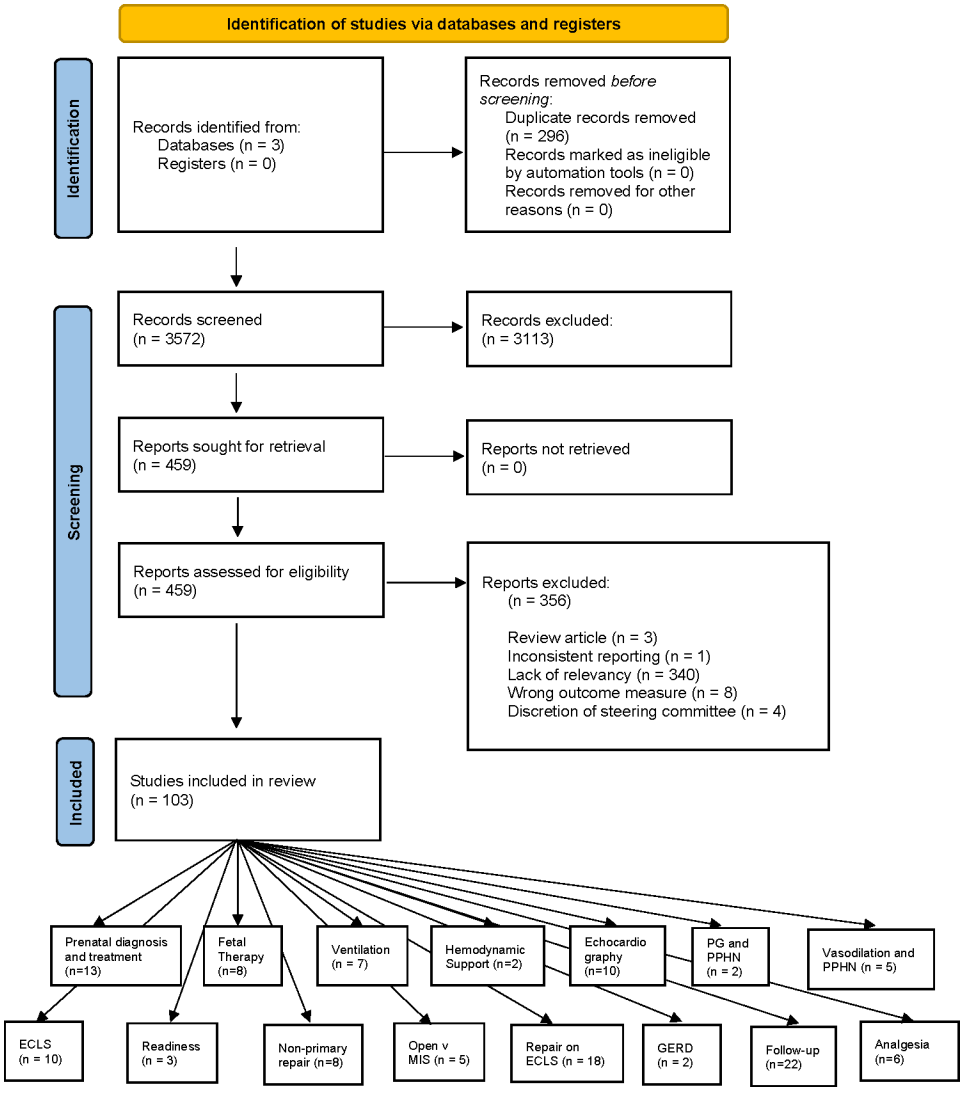

Figure 1 PRISMA flow diagram. ECLS, extracorporeal life support; GERD, gastro-oesophageal reflux disease; MIS, minimally invasive surgery; PG, prostaglandin; PPHN, persistent pulmonary hypertension of the newborn; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Level A
· High-quality evidence from more than 1 RCT · Meta-analyses of high-quality RCTs · One or more RCTs corroborated by high-quality registry studies
Level B-R (Randomized)
· Moderate-quality evidence from 1 or more RCTs · Meta-analyses of moderate-quality RCTs
Level B-NR (Non-randomized)
· Moderate-quality evidence from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies · Meta-analyses of such studies
Level C-LD (Limited data)
· Randomized or nonrandomized observational or registry studies with limitations of design or execution · Meta-analyses of such studies · Physiological or mechanistic studies in human subjects
Level C-EO (Expert Opinion)
· Consensus of expert opinion based on clinical experience

Figure 2 Taxonomy of the levels of evidence used to grade recommendations.[1] RCTs, randomised controlled trials.

6. Role of prostaglandins in the management of CDH-associated pulmonary hypertension.
7. Targeted pulmonary vasodilation in CDH-associated pulmonary hypertension.
8. Role of extracorporeal life support (ECLS).
9. Surgical readiness.
10. Options for non-primary surgical repair.
11. Open versus minimally invasive surgical repair.
12. Surgical repair on ECLS.
13. Management of gastro-oesophageal reflux.
14. Long-term follow-up.
15. Analgesia, sedation and neuromuscular blockade.

RESULTS

Twenty CDH care recommendations were updated, and 15 new recommendations were added. These are presented below, categorised by the 15 care areas in CDH management.

Prenatal diagnosis and management

Prenatally diagnosed CDH is associated with additional structural and genetic anomalies in 30–40% of cases,[4 5] most commonly cardiovascular malformations.[6] All antenatally detected cases of CDH should undergo a detailed anatomical survey and fetal echocardiogram in a tertiary fetal medicine centre. All affected pregnancies should be offered invasive genetic testing with chromosomal microarray analysis (CMA) given a 10–13% risk of CMA abnormality in isolated CDH.[7 8] Expanded genomic analysis (eg, exome sequencing, RNA analysis) will likely increase this diagnostic yield further[9 10] (table 1).

Antenatal sonographic predictors of neonatal survival include the observed-to-expected lung-to-head ratio (o/e LHR)[11–13] and intrathoracic liver herniation.[13–15] The o/e LHR should be measured with the trace method (figure 4) between 22 and 32 weeks' gestational age (GA)[13 16 17] in experienced centres.[18 19] Severe pulmonary hypoplasia is predicted by an o/e LHR of ≤25% in left CDH and o/e LHR ≤50% for right CDH,[20] with estimated survival of ≤30%[11 12 21] and 20%[20] for left and right CDH, respectively. Moderate pulmonary hypoplasia is defined as an o/e LHR of 26–34% in left CDH. Intrathoracic liver herniation may be challenging to recognise sonographically. As such, stomach position classification has been proposed as a surrogate,[22–25] and has been shown to correlate with neonatal mortality and morbidity.[23 24 26] Although promising in its simplicity, this prognosticator requires further prospective validation.

Fetal magnetic resonance imaging (MRI) provides additional prognostic information by assessing the o/e total fetal lung volume (o/e TFLV)[27] and quantifying liver herniation.[28 29] An o/e TFLV<35% and intrathoracic liver herniation are significant predictors of mortality.[11 13 27–29] When compared with ultrasound (US), MRI is more reproducible and is not limited by maternal habitus or fetal position. Additionally, MRI parameters perform better, with greater sensitivity and specificity for survival prediction.[30] Based on the protocol from the TOTAL trial,[21] as well as current practice in most centres performing fetal tracheal occlusion, the ideal timing for MRI appears to be around 26 weeks since earlier timing may lead to inaccurate measurements. Combined, o/e TFLV and liver herniation demonstrate better predictive value for mortality and need for ECLS.[29] Although MRI may be advantageous for prenatal prognostication, US assessment is likely to remain the cornerstone of antenatal prognostication due to its widespread availability. Both imaging modalities should be used together, particularly in high-risk fetuses.

Agreement with recommendation:
1) Strongly agree
2) Somewhat agree
3) Neither agree or disagree
4) Somewhat disagree
5) Strongly disagree

Level of Consensus	Description
4	**STRONG AGREEMENT** with recommendation: >80% #1 or #5
3	**GOOD AGREEMENT** with recommendation: >80% of #1 + #2 or #4 + #5 but >50% of the votes as #1 or #5
2	**WEAK AGREEMENT** with recommendation: >80% of #1 + #2 or #4 + #5 but <50% of the votes as #1 or #5
1	**NO CONSENSUS**

Figure 3 Consensus framework.[1]

Table 1 Updated and new recommendations regarding prenatal diagnosis and management of CDH[7–10 13 16 18 20 26 32 152–154]

Updated recommendations	Strength of consensus	Level of evidence
1.1 Ultrasound measurement of o/e LHR using the trace method should be obtained between 22 and 32 weeks' GA, in consultation with a regional fetal medicine/therapy programme.	4	B-NR
1.2 Observed/expected LHR cut-offs of ≤25% and ≤50% should be used to predict poor outcome for left and right CDH, respectively.	4	B-NR
1.3 MRI for the assessment of o/e TFLV and liver herniation should be considered in all fetuses with CDH, and is strongly recommended in fetuses with severe or moderate CDH by o/e LHR, ideally in collaboration with a fetal therapy programme.	4	B-NR
New recommendations	**Strength of consensus**	**Level of evidence**
1.4 Due to the increased risk of associated structural anomalies, a detailed anatomy assessment and a fetal echocardiogram should be performed in a tertiary fetal medicine centre for all pregnancies with prenatally diagnosed CDH.	3	B-NR
1.5 Invasive antenatal genetic testing, ideally with chromosomal microarray analysis, should be offered in all CDH pregnancies.	4	B-NR
1.6 Delivery at ~39 weeks gestation should be considered, with delivery planning in a tertiary centre experienced in the management of CDH with NICU, PICU and paediatric surgery expertise. Mode of delivery should be determined based on standard obstetric indications.	4	B-NR

CDH, congenital diaphragmatic hernia; GA, gestational age; NICU, neonatal intensive care unit; NR, non-randomised; o/e LHR, observed-to-expected lung-to-head ratio; o/e TFLV, observed-to-expected total fetal lung volume; PICU, paediatric intensive care unit.

Delivery is recommended in a tertiary care centre with neonatal intensive care unit (NICU) and paediatric surgery expertise in CDH management, as outborn delivery is a significant predictor of mortality.[31] Mode of delivery should be determined on usual obstetric grounds, and should be considered between 38 and 39 weeks' gestation due to reportedly improved survival at 28 days with term delivery.[32]

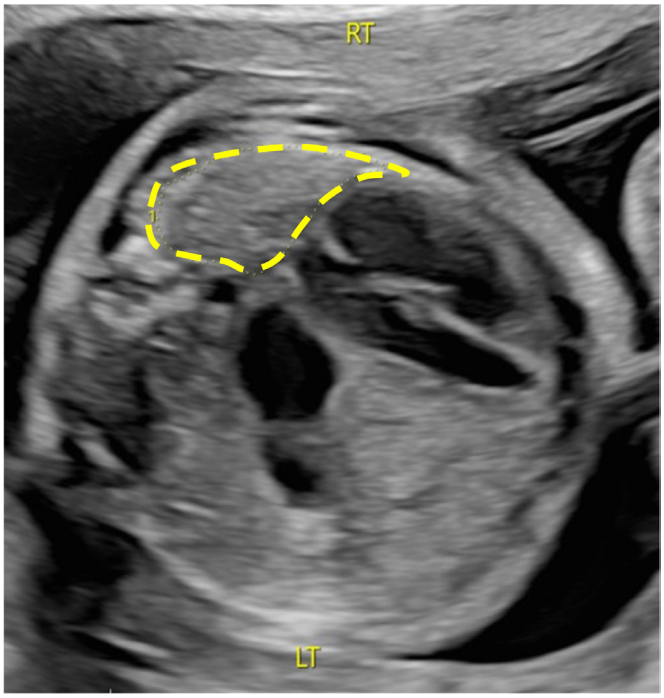

Figure 4 Axial section of the fetal chest demonstrating sonographic measurement of the right (RT) lung area using the 'trace' method in a fetus with left CDH. The lung area is obtained on a well-optimised cross-section of the fetal chest at the level of the four-chamber view of the heart, by manually tracing the lung perimeters. The lung area is combined with the fetal head circumference to obtain an observed-to-expected lung-to-head ratio. CDH, congenital diaphragmatic hernia; LT, left.

Fetal therapy in CDH

Due to the significant morbidity and mortality associated with CDH, fetal interventions aimed at improving lung development in utero have been investigated.[33–35] Fetal endoscopic tracheal occlusion (FETO), a minimally invasive percutaneous procedure that prevents egress of fetal fluid and consequent accelerated airway and pulmonary vessel growth, has shown promise.[36] In both multicentre and single-centre cohort studies, FETO has demonstrated statistically improved survival for left and right CDH.[20 37–40] The Tracheal Occlusion to Accelerate Lung growth (TOTAL) randomised controlled trials (RCTs) evaluated the impact of FETO on survival in isolated left CDH predictive of both moderate (o/e LHR 25–35% or o/e LHR 35–45% with liver herniation)[41] and severe (o/e LHR <25%) pulmonary hypoplasia, in comparison with standard neonatal management.[21] In the 'severe' trial, a significant improvement in survival to discharge (40% vs 15%; p=0.009) was noted with FETO insertion at 27–29 weeks' gestation compared with expectant management, despite an increased incidence of preterm premature rupture of membranes (PPROM; 47% vs 11%) and preterm birth (75% vs 29%). Despite later FETO at 30–32 weeks' gestation in the moderate trial, there was also an increased incidence of PPROM (44% vs 12%) and preterm birth (64% vs 22%), without an improvement in survival (63% vs 50%; p=0.06).[41] Pooled data from both trials were reanalysed to evaluate the heterogeneity of treatment effect by o/e LHR and GA at balloon insertion, and found no evidence of effect by o/e LHR. Rather, the differences in results between trials were likely due to later balloon insertion in the moderate trial[42] (table 2).

Table 2 New recommendations regarding fetal therapy in CDH[20 21 39–42 44 45]

New recommendations	Strength of consensus	Level of evidence
2.1 Fetal endoscopic tracheal occlusion (FETO) should be considered a treatment option and discussed with parents for all cases of severe CDH.	4	A
2.2 FETO may be considered as a treatment option for moderately severe CDH.	4	B-R

CDH, congenital diaphragmatic hernia; R, randomised.

Based on these studies, FETO is an option for severe, and possibly moderate risk CDH in selected patients, with more research required for its use in infants with moderate CDH. Discussions regarding FETO lend themselves to a shared decision-making approach with families. It is important to consider potential burdens and issues of healthcare access for family and caregivers related to maternal risks, distance and displacement from home for the duration of treatment (since FETO is only offered in very select centres with extensive fetoscopic experience), and the impact on the family unit, particularly with respect to disruption of the support structure, occupation and wages/income. Further studies are also needed to evaluate the impact of prematurity on neonatal morbidity and long-term outcomes following FETO therapy.

Research addressing the prevention of pulmonary hypertension using antenatal sildenafil has been promising, with animal studies demonstrating some rescue of the pulmonary vascular bed and improved airway morphometry with transplacental sildenafil therapy.[43 44] Trials are ongoing to evaluate the transplacental transfer and safety of sildenafil in humans,[45] which may lead to a randomised trial of antenatal sildenafil for pulmonary hypertension mitigation.

Ventilation in CDH

Airway management at birth

The neonatal resuscitation guideline from the American Heart Association and the American Academy of Pediatrics supports immediate endotracheal intubation for neonates with a known diagnosis of CDH and the avoidance of bag–valve–mask ventilation.[46] A small, retrospective audit found that a spontaneous breathing approach was successful in 40% of infants with mild CDH (o/e LHR >50%), although half of the successful cases required non-invasive ventilation with its attendant risk of hollow visceral insufflation.[47] Survival to discharge and total duration of postoperative ventilation were identical regardless of whether or not the trial of spontaneous breathing was successful. This new evidence is insufficient to lead to a revision of the current recommendation (table 3).

Mode of ventilation

The VICI trial[48] attempted to provide level I evidence regarding the initial ventilatory mode in CDH. Analysis of the 171 of 356 targeted patients showed similar rates of mortality and bronchopulmonary dysplasia between groups initially managed with conventional mechanical ventilation (CMV) versus high-frequency oscillatory ventilation (HFOV).

Two retrospective studies comparing conventional ventilation with high-frequency ventilation (HFV) were unable to show any difference in survival, need for inhaled nitric oxide (iNO), duration of mechanical ventilation or oxygen requirement at discharge. The study by Derraugh *et al*[49] was based on experience at a single non-ECLS centre over a 25-year period. The HFV group included patients managed with both high-frequency jet ventilation and HFOV. A Japanese CDH Study Group analysis compared 250 HFOV with 77 CMV CDH patients.[50] Both studies suggested that physicians are more likely to choose HFV in sicker, higher-risk patients.

Individual, single-centre retrospective studies have demonstrated that high-frequency positive pressure ventilation,[51] neurally adjusted ventilatory assist[52 53] and heliox admixture with oxygen[54] hold some promise for future CDH management.

Fundamentals of haemodynamic support

In the setting of haemodynamic instability, treatment to optimise perfusion is centred around very judicious fluid resuscitation and early inotropic support to prevent pulmonary oedema. Indeed, ventricular dysfunction is a major contributor to persistent hypotension which will only be exacerbated by excessive fluid resuscitation. While the choice of inotropic agent depends on the clinical state of the infant with CDH, dopamine, epinephrine and norepinephrine are still considered the first-line choices for cardiac or vasopressor support.[55] Higher dosing of epinephrine may cause adverse events such as tachyarrhythmia, hyperglycaemia and lactic acidosis due to a dose-dependent shift from beta to alpha-receptor agonist. Norepinephrine only has vasomotor effects and increasing afterload could further impair already precarious cardiac function. Furthermore, norepinephrine may also potentially increase pulmonary arterial resistance. While there is some recent evidence suggesting that dopamine may be an inferior choice based on experience extrapolated from infants with non-CDH persistent pulmonary hypertension,[56] dopamine is still the most extensively used inotropic medication in the neonatal literature, and possesses a well-documented safety profile.[57] As such, there is no conclusive evidence demonstrating the superiority of lesser-studied agents over dopamine in the population with CDH. However, vasopressin is showing promise in supporting systemic haemodynamics in catecholamine-resistant shock states without affecting pulmonary haemodynamics based on a small, retrospective study of 13 infants with CDH.[58] Cardiovascular management, as well as the introduction, discontinuation and precise titration of each agent, should occur within a framework of targeted haemodynamic management. Treatment will need to be individualised to meet the unique requirements and responses of each neonate and their specific cardiovascular status (table 4).

There is accumulating evidence that the underlying cardiovascular phenotype may vary among different patients with CDH.

Table 3 Unchanged recommendations regarding ventilation in CDH[47 49–54]

Unchanged recommendations	Strength of consensus	Level of evidence
3.1 All newborns with CDH who require respiratory support should be intubated (for assisted ventilation) immediately after birth.	4	C-EO
3.2 A T-piece on the bag–valve mask, or a ventilator, should be used to rigorously avoid a peak inspiratory pressure (PIP) greater than 25 cm H_2O from the first breaths onwards in all newborns with CDH.	4	B-NR
3.3 Gentle intermittent mandatory ventilation (IMV) should be the initial mode of ventilation for all newborns with CDH requiring respiratory support. High-frequency oscillatory ventilation or high-frequency jet ventilation should be used as rescue therapy when the PIP required to control hypercapnia using IMV exceeds 25 cm H_2O.	4	B-R
3.4 An arterial pCO_2 (partial pressure of carbon dioxide) between 45 and 60 mm Hg and a pH between 7.25 and 7.40 should be targeted in all newborns with CDH.	4	B-NR
3.5 Supplemental oxygen should be titrated to achieve a preductal saturation of at least 85%, but not >95%.	4	C-EO

CDH, congenital diaphragmatic hernia; EO, expert opinion; NR, non-randomised; R, randomised.

Table 4 Unchanged recommendations regarding the fundamentals of haemodynamic support in CDH[65 67]

Unchanged recommendations	Strength of consensus	Level of evidence
4.1 If poor perfusion persists, cardiac function should be assessed by echocardiography.	4	B-NR
4.2 Hydrocortisone should be used to treat hypotension that responds inadequately to intravenous volume and vasopressor therapy.	4	B-NR
Updated recommendations	**Strength of consensus**	**Level of evidence**
4.3 Treatment of poor perfusion (any combination of capillary refill >3 s, lactate >3 mmol/L, urine output <1 mL/kg/hour) and blood pressure below norms for age should include: a. Very judicious administration of crystalloid, if any, and generally not exceeding 20 mL/kg. b. Inotropic agents such as dopamine, epinephrine or norepinephrine.	4	B-NR

CDH, congenital diaphragmatic hernia; NR, non-randomised.

This phenotype may evolve during the early acute phase of hospital admission, underscoring the need for continuous, multidisciplinary vigilance and the utilisation of multimodal clinical information that includes bedside echocardiography.[59 60] Nevertheless, although diverse phenotypes have been documented, no trials within CDH cohorts have delineated the benefits of employing specific cardiovascular management strategies for acute pulmonary hypertension, right ventricular dysfunction, left ventricular dysfunction or biventricular dysfunction in this population. Hence, clinicians should tailor their therapy based on their best assessment of the patient's underlying physiology.[61–63]

Acute kidney injury (AKI) is defined and staged using the Neonatal Modified Kidney Disease: Improving Global Outcomes[64] Serum Creatinine criteria. A few retrospective studies confirmed that AKI is common among infants with CDH.[65–67] Among those with AKI, survival in these series ranged from 37% to 47%, and an increasing stage of AKI was associated with decreased survival. The authors found that AKI in patients with CDH was associated with prenatal risk factors, including lower antenatal lung volumes, liver herniation and postnatal factors such as vancomycin, corticosteroids and diuretic use, abdominal closure surgery, hypotension and elevated plasma-free haemoglobin. The situation is further complicated in patients receiving ECLS who are prone to fluid overload and a systemic inflammatory response that can also lead to AKI. Infants who remain unstable despite fluid and vasopressor therapy should receive hydrocortisone as well as echocardiographic assessment of cardiac function.

The role of echocardiography in CDH

Echocardiography is recommended shortly after birth, not only to verify suspected cardiac anomalies based on fetal echocardiography but also to (a) assess cardiac dimensions and ventricular function, (b) estimate pulmonary arterial pressures, (c) assess for shunt physiology and (d) guide/adjust cardiovascular support. A minimum of two standardised echocardiograms are recommended. The first should occur within the first 24–48 hours of life (or preoperatively), with earlier evaluation recommended for high-risk infants or in the context of severe postnatal cardiorespiratory instability as it may dictate additional interventions or the timing of surgery. This may be particularly important in anticipation of ECLS candidacy.[68 69] Interestingly, Yang *et al*[68] demonstrated reduced inotrope usage, lower ECLS rates, repair at earlier age and improved survival using a care bundle that deferred echocardiography until after 24 hours (or alternatively a time-limited assessment) to avoid excessive manipulation during the critical first 24 hours of physiological transition. The second echocardiogram should occur at 2–3 weeks of life, to assess for persistence of pulmonary hypertension or cardiac dysfunction. Additional studies may be conducted as clinically indicated (eg, pre-surgery or pre-discharge). This is especially relevant in the presence of significant pulmonary hypertension or cardiac dysfunction since this has been associated with adverse outcomes and may affect surgical and anaesthetic preparation.[70–72] Two single-centre studies highlight a possible prognostic role for pulmonary artery acceleration time to right ventricular ejection time (PAAT/ET) for early risk assessment in neonates with CDH. PAAT/ET values at the baseline echocardiogram are significantly lower in ECLS patients compared with non-ECLS patients. Additionally, ECLS non-survivors demonstrate lower PAAT/ET values at 5–7 days of life when compared with ECLS survivors.[73 74] These results suggest the utility of echocardiography at 5–7 days of life during ECLS support (table 5).

The measurement of brain natriuretic peptide (BNP) or N-terminal BNP may serve as adjunct biomarkers to detect underlying cardiac strain[75]; increasing trends in these biomarkers have been

Table 5 Updated and new recommendations regarding the use of echocardiography in CDH[68–77]

Updated recommendations	Strength of consensus	Level of evidence
5.1 A minimum of two standardised echocardiograms should be performed, one within 24–48 hours of life (or preoperatively) and another at 2–3 weeks of life, to assess pulmonary hypertension and cardiac function. Additional studies may be conducted as clinically indicated.	4	B-NR
5.2 While initial echocardiography may be deferred after 24 hours to avoid excessive manipulation during the critical period of pulmonary vascular adaptation, early (<24 hours) echocardiography should be considered in the context of severe cardiorespiratory instability.	4	B-NR
New recommendation	**Strength of consensus**	**Level of evidence**
5.3 Repeat echocardiography on days of life 5–7, especially when on ECLS support, may be indicated to assess progression or improvement of pulmonary hypertension.	4	C-LD

CDH, congenital diaphragmatic hernia; LD, limited data; NR, non-randomised.

Table 6 Updated recommendations regarding the role of prostaglandin E1 (PGE1) in the medical management of pulmonary hypertension associated with CDH[78 79]

Updated recommendations	Strength of consensus	Level of evidence
6.1 PGE1 infusions should be used: a. If pulmonary or systemic blood flow is dependent on patency of the ductus arteriosus. b. In the presence of a concomitant anatomical cardiac lesion.	4	B-NR
6.2 PGE1 infusions may be considered: a. In the presence of supra-systemic right ventricular pressures. b. In the presence of right ventricular failure. c. If right-to-left ductal shunting exceeds left-to-right shunting.	4	C-LD
6.3 PGE1 should be considered to maintain ductal patency in CDH if there is left ventricular dysfunction or functional aortic atresia in the context of systemic right ventricular or pulmonary artery pressures.	4	C-EO

CDH, congenital diaphragmatic hernia; EO, expert opinion; LD, limited data; NR, non-randomised.

associated with adverse CDH outcomes (death or respiratory support at 56 days of life).[76 77] However, institutional availability of these markers may vary and there is a paucity of data indicating improvement of outcomes solely based on biomarker surveillance.

The role of prostaglandins in the management of CDH-associated pulmonary hypertension

Two small, retrospective studies reviewed the impact of prostaglandin E1 (PGE1) in the management of severe pulmonary hypertension in CDH and were the basis for changes to existing recommendations. Le Duc *et al* noted improvement in preductal and post-ductal saturations, as well as increased ductal blood flow and a reduction in fractional inspired oxygen with PGE1.[78] Lawrence *et al*[79] demonstrated improved echocardiographic indices as well as reduced BNP levels in 57 patients with PGE1.[79] Both studies supported the use of PGE1 in the context of a restrictive ductus arteriosus, severe pulmonary hypertension and impending right ventricular failure (table 6).

The use of 'targeted' pulmonary vasodilation in the management of CDH-associated pulmonary hypertension

The use of targeted pulmonary vasodilator therapy is recommended in the context of CDH-associated pulmonary hypertension when standard cardiorespiratory manoeuvres fail to maintain adequate oxygenation or cardiac function. iNO may be considered as part of the treatment regimen but only in the context of demonstrable echocardiographic and clinical evidence of improvement, which, if lacking, should lead to its cessation. Milrinone is a lusitropic medication that theoretically enhances diastolic function while also causing pulmonary and systemic vascular dilation. It undergoes renal excretion and can offer assistance to a compromised left ventricle. Milrinone is recommended for its pulmonary arterial vasodilator properties based on experience extrapolated from non-CDH, cardiac infants with pulmonary hypertension,[1] with caution for its use in the context of hypotension. The results of an ongoing RCT should clarify milrinone use in the population with CDH.[80] Prostaglandins (such as treprostinil and epoprostenol) and vasopressin[81] may be considered as rescue therapy for pulmonary hypertension in newborns with CDH prior, during or after ECLS.[77 82–84] Responders to these therapies have been reported, although it should not delay the initiation of other life-saving strategies (such as ECLS) in infants with severe hypoxic respiratory failure already meeting criteria (table 7).

The role of ECLS in the management of CDH

A recent guideline statement from the Extracorporeal Life Support Organization (ELSO) was published without clear adherence to GRADE methodological standards.[69] ELSO generated 26 recommendations in relation to CDH management, many of which overlap considerably with recommendations included here. The Collaborative's author group specifically endorses the ELSO indications for initiation of ECLS based on hypoxic or hypercapnic respiratory failure, circulatory failure or acute clinical deterioration[69] (table 8).

There continues to be sparse evidence that ECLS confers a survival advantage in CDH. A large retrospective cohort study demonstrated that overall mortality was higher when ECLS was used in CDH. A survival advantage was only observed in a

Table 7 Updated and new recommendations regarding targeted pulmonary vasodilation in the management of CDH-associated pulmonary hypertension[77 82–84 155]

Unchanged recommendations	Strength of consensus	Level of evidence
7.1 In the context of echocardiographic confirmation of supra-systemic pulmonary arterial hypertension in the absence of left ventricular dysfunction, a trial of inhaled nitric oxide (iNO) should be used, providing that lung recruitment is adequate. If there is no iNO response based on echocardiographic assessment or other parameters (clinical or laboratory), iNO should be stopped.	4	B-NR
7.2 Milrinone should be used to treat cardiac dysfunction, particularly if it is associated with pulmonary hypertension.	4	B-NR
7.3 The use of sildenafil may be considered in patients with refractory pulmonary hypertension (ie, unresponsive to iNO) or as an adjunct when weaning iNO.	3	B-NR
New recommendation	**Strength of consensus**	**Level of evidence**
7.4 The use of prostacyclin (such as treprostinil and epoprostenol) may be considered as rescue therapy prior, during or after ECLS in infants with severe and refractory pulmonary hypertension.	3	C-LD

CDH, congenital diaphragmatic hernia; ECLS, extracorporeal life support; LD, limited data; NR, non-randomised.

Table 9 Unchanged and new recommendations regarding surgical readiness criteria for CDH[94–96]

Unchanged recommendations	Strength of consensus	Level of evidence
9.1 The following criteria should be met prior to surgery: urine output >1 mL/kg/hour, FiO_2 <0.5, preductal oxygen saturation between 85% and 95%, normal mean arterial pressure for gestational age, lactate <3 mmol/L and estimated pulmonary artery pressures less than systemic.	4	B-NR
9.2 Surgery should be reconsidered if a patient fails to meet surgical readiness criteria after 2 weeks.	4	C-LD
New recommendation	**Strength of consensus**	**Level of evidence**
9.3 In patients who have achieved physiological stability, there is no benefit in delaying operative repair.	4	C-LD

CDH, congenital diaphragmatic hernia; FiO_2, fractional inspired oxygen; LD, limited data; NR, non-randomised.

subgroup of high-risk patients and only in high-volume centres. This and another small centre series suggest that high-risk patients with CDH might have lower mortality when ECLS is used.[85 86] Two recent studies have considered the cost and societal implications of prolonged ECLS runs for CDH, arguing strongly against indefinite run length.[87 88]

There is accruing evidence regarding current age (<34 weeks' gestation) and weight (<1.7–2 kg) exclusion criteria for ECLS, suggesting they be reconsidered under special circumstances. A systematic review of all premature patients treated with ECLS demonstrated that survival rates for premature babies with CDH supported with ECLS, although rarely offered, were similar to survival in the prematurely born infant with CDH without ECLS.[89 90] The most recent ELSO dataset demonstrates an overall survival of 50% (n=7564), with a modest decline in infants <34 weeks' GA (44%); survival is even lower in those infants <2 kg (29%). Given the high risk of death and neural impairment associated with ECLS use in this population,[91] the provision of ECLS to populations with CDH with traditional relative contraindications should remain experimental and only contemplated at high-volume ECLS centres.

Two recent investigations reviewed repeat ECLS for CDH, with a combined total n=31.[92 93] Both papers endorsed repeat ECLS, with cannulation criteria remaining similar to the criteria used for the index cannulation. While it is clear that patients with CDH who undergo ECLS have inferior developmental/cognitive outcomes than a non-ECLS cohort, it is unknown whether a second run further compounds this impairment.

Surgical readiness criteria

Delaying surgical repair until 'physiological stability' has been achieved (usually interpreted as cardiorespiratory function and oxygenation sufficient to avoid lactic acidosis with evidence of subsystemic pulmonary artery pressure) appears to optimise CDH outcome. A recent retrospective, single-centre study of 158 neonates with CDH studied temporal trends in oxygenation index (OI) as a proxy for physiological stability. OI measurements in the first 24 hours of life corresponded with mean preoperative OI values suggesting that early OI could be used to determine the timing of operative repair in CDH. An OI <9.4 correlated with survival, and any delay in surgical repair after an OI of <9.4 was achieved led to increased ventilator days and delayed hospital discharge.[94] These findings suggest that there is no benefit to delaying surgical repair once clinical stability has been attained. A smaller prospective study from China (n=30) also concluded that delaying thoracoscopic repair beyond 48 hours was of no benefit for mild-moderate CDH (LHR >1)[95] (table 9).

One additional study demonstrated that meaningful survival can be achieved in high-risk patients and reinforced the importance of avoiding non-repair whenever possible. In their study exploring differences in outcomes at high-volume centres, Harting *et al*, noted that centres that had low rates of non-repair had higher survival than those centres with high rates of non-repair (suggesting survivability of repaired, highest-risk patients).[96]

Table 8 Updated recommendation regarding the use of ECLS in CDH[69 85–93]

Updated recommendation	Strength of consensus	Level of evidence
8.1 ECLS may be considered in populations with CDH with traditional size/age or comorbidity contraindications under special circumstances.	2	C-LD

CDH, congenital diaphragmatic hernia; ECLS, extracorporeal life support; LD, limited data.

Options for non-primary repair

Although there is no clearly preferred prosthetic (synthetic or biological) patch material for the repair of defects not amenable to primary repair,[97–101] recent studies describe success with defect closure using autologous muscle flaps. Two studies of 97 (in aggregate) neonates with CDH with large defects closed with oblique muscle flaps recorded 5-year recurrence rates of 3% and 3.5%.[102 103] Rates of repair on ECLS were similar to those undergoing patch repair (39% vs 31%) and complication rates, including bleeding on ECLS, were similar between groups—an observation made separately in another publication.[104] Three earlier publications reported an additional 50 muscle flap repairs, from which there were 3 reported recurrences (6%).[105–107] Long-term musculoskeletal outcomes (scoliosis, chest wall deformities) were equivalent in patch versus muscle flap groups[107] (table 10).

Open versus minimally invasive repair

Any consideration of a minimally invasive approach to CDH repair must acknowledge its higher recurrence rate compared with open and the importance of selecting patients based on favourable ventilatory and pulmonary hypertension preoperative parameters. Five recent cohort studies (totalling 137 patients) have reported recurrence rates of 7–21% after thoracoscopic repair (TR) of neonatal CDH.[108–111] Low-quality evidence suggests that use of a biological mesh underlay for primary and prosthetic mesh repairs reduces both the risk of recurrence and adhesive bowel obstruction[112] (table 11).

An earlier multicentre study of 37 infants undergoing TR identified preoperative OI >3 as independently predictive of

Table 10 Unchanged and new recommendations regarding non-primary repair in CDH[97–104]

Unchanged recommendation	Strength of consensus	Level of evidence
10.1 For diaphragmatic defects that are not amenable to primary repair, oversized, tension-free polytetrafluoroethylene (GORE-TEX) patches should be used.	4	C-LD
New recommendation	**Strength of consensus**	**Level of evidence**
10.2 Oblique muscle flap repair may be considered if technical expertise with the procedure exists.	4	C-LD

CDH, congenital diaphragmatic hernia; LD, limited data.

treatment failure, defined as need for conversion or the development of a serious postoperative complication.[113]

Surgical repair on ECLS

Survival to discharge for infants with CDH who require ECLS is approximately 50%, with single centres reporting rates approaching 70%.[86] Complications of repair on ECLS are predominantly metabolic, circuit related or haemorrhagic (including surgical site), which occurs in 25% of cases and is only partially offset by surgical technique and modified anticoagulation.[114] CDH non-repair rates in infants who receive ECLS are approximately 15%,[115] a rate which could be reduced by an on-ECLS repair strategy (table 12).

Two large registry studies have investigated the relationship between on or after ECLS CDH repair and survival. A Congenital Diaphragmatic Hernia Study Group (CDHSG) study of propensity-matched patients showed a survival advantage (HR 0.54 (0.38, 0.77)) to repair on ECLS, with high-volume centres disproportionately represented in this group.[116] However, if non-repairs were excluded, the survival benefit was reversed. An ELSO registry study of >2200 propensity-matched patients which excluded non-repairs demonstrated a threefold increased mortality and a run duration-dependent increased risk of severe neurological injury in the on-ECLS repair group.[117] A comparative study from Ann Arbor demonstrated the highest survival rate (94%) in infants who were decannulated prior to repair.[118]

Studies have explored outcomes according to early or late repair on ECLS with conflicting results. Two studies from CDHSG have shown improved survival with early repair, defined as <72 hours, or within the shortest time to repair quartile range.[116 119] In addition, a single-institution study of 33 patients comparing repair within 24 hours of cannulation versus repair between 24 hours and 72 hours demonstrated improved survival in the <24-hour group.[120] Conversely, a single-institution study comparing early (≤5 days) versus late (>5 days) repair protocols demonstrated that early repair was independently predictive of mortality (HR 3.48, CI 1.28 to 9.45).[118]

A single-centre study recently reported 2-year neurocognitive outcomes in CDH survivors repaired on ECLS versus after or without ECLS. While the entire CDH cohort had neurocognitive scores that were significantly lower than population norms in all domains, those repaired on ECLS had lower cognitive and motor scores compared with those repaired after ECLS.[121]

These analyses suggest that the relationship between survival and timing of repair relative to the ECLS run is confounded by whether mortality associated with non-repair (which will be more likely in high-risk patients) is excluded or attributed to the after-ECLS group. Patients with adverse prenatal predictors who go onto ECLS with severe cardiopulmonary derangement represent the greatest risk of non-repair. Consideration should be given to early repair in these patients.

Management of gastro-oesophageal reflux in CDH

Gastro-oesophageal reflux disease (GERD) is extremely prevalent with formal impedance testing demonstrating persistence of GERD in >60% of infants with CDH beyond 1 year of age.[122] This has led to consideration of 'preventative' fundoplication, which was explored in a prospective, multi-institutional study from France in which select institutions performed preventative fundoplication (n=27; 11%) versus no fundoplication for

Table 11 Updated recommendation regarding the type of surgical repair in CDH[108–112]

Updated recommendation	Strength of consensus	Level of evidence
11.1 Although recurrence rates for minimally invasive repairs of CDH continue to be higher than open repairs, minimally invasive repair may be considered in patients: a. Who easily achieve preoperative ventilatory targets. b. With infrasystemic pulmonary artery pressures and normal cardiac function. c. If the surgical team is technically proficient and the anaesthetic team is experienced and able to continuously monitor and manage intraoperative hypercarbia and acidosis.	3	C-LD

CDH, congenital diaphragmatic hernia; LD, limited data.

Table 12 Unchanged and updated recommendations regarding surgical repair on ECLS[86 114 116–120]

Unchanged recommendation	Strength of consensus	Level of evidence
12.1 For patients on ECLS, surgery should be avoided until after decannulation.	3	B-NR
Updated recommendation	**Strength of consensus**	**Level of evidence**
12.2 Patients with a low probability of survival based on prenatal predictors or the severity of cardiopulmonary derangement at cannulation are at risk of failure to wean and may benefit from early repair.	3	B-NR

ECLS, extracorporeal life support; NR, non-randomised.

Table 13 Updated recommendation regarding the management of gastro-oesophageal reflux in CDH[122 123]

Updated recommendation	Strength of consensus	Level of evidence
13.1 Routine 'preventative' fundoplication is not indicated at the time of diaphragm repair.	4	B-NR

CDH, congenital diaphragmatic hernia; NR, non-randomised.

high-risk cases at the time of CDH repair with prosthetic patch.[123] The rate of redo fundoplication in the preventative group was higher than the rate of subsequent fundoplication for medically refractory GERD in the no fundoplication group. Moreover, preventative fundoplication patients experienced significantly longer hospital stays and additional morbidity including oral aversion and the need for tube feeding >6 months. Thus, there is no advantage to fundoplication at the time of CDH repair; it should only be considered in the context of failed medical management (table 13).

Long-term follow-up in CDH

Studies continue to deepen our understanding of the long-term sequelae of CDH beyond the initial NICU admission along a number of biophysical domains, including cardiopulmonary,[124–131] gastrointestinal/nutrition/growth,[127 132–136] neurodevelopmental,[126 128 132 137–140] musculoskeletal[128 141] and all-cause late mortality.[142] These findings reinforce the importance of longitudinal follow-up by a team with CDH-specific expertise in accordance with the American Academy of Pediatrics guidelines. Finally, there is a significant knowledge gap in the optimal transitioning of patients with CDH from a paediatric to adult care context (table 14).

Pain, analgesia and neuromuscular blockade management in CDH

A systematic review and subsequent clinical guidelines for analgesia and sedation in term and near-term infants requiring mechanical ventilation made recommendations for infants with severe respiratory failure, which apply to patients with CDH: (1) a validated pain score[143] should be used to titrate opioid dose (strong recommendation); (2) fentanyl as a continuous infusion (CI) is preferred over morphine in presence of hypotension or renal failure (conditional recommendation); (3) when tolerance with one agent has occurred, opioids should be rotated (conditional recommendation); (4) use of short-acting benzodiazepine as bolus or CI can help reduce dose of opioid or need for muscle relaxant (conditional recommendation).[144] Use of fentanyl as a CI is also supported by a neonatal RCT that demonstrated favourable pharmacokinetics and equivalent pain scores versus intermittent bolus dosing[145] (table 15).

There is increasing evidence supporting use of intravenous and enteral acetaminophen or paracetamol in postoperative CDH management. Its use was reported in 48% of post-repair patients in the Children's Hospital Neonatal Consortium (CHNC) CDH Database.[146] A Cochrane review demonstrated that use of paracetamol decreased opioid utilisation in infants undergoing painful procedures or following invasive surgery.[147] An RCT and subsequent implementation cohort study demonstrated reduced opioid utilisation and equivalent pain scores in patients undergoing non-cardiac surgery managed postoperatively with opioids combined with either paracetamol or placebo.[148 149] A recent quality improvement study demonstrated that a standardised protocol which combined intravenous acetaminophen, education and standardised pain handover reduced postoperative opioid use and duration of intubation in patients with CDH.[150]

Table 14 Updated and new recommendations regarding long-term follow-up in CDH[124–142]

Updated recommendations	Strength of consensus	Level of evidence
14.1 We recommend standardised multidisciplinary follow-up for children with CDH to provide surveillance and screening, optimal and timely diagnosis and clinical care adjusted to the level of risk.	4	B-NR
14.2 We recommend identifying the subset of CDH survivors at high risk of long-term morbidity as comprising those infants and children who require extracorporeal life support, who have been repaired with a patch or muscle flap or who require respiratory support at 30 days of life.	4	B-NR
New recommendation		
14.3 Where possible, the following members should constitute the longitudinal multidisciplinary follow-up team for CDH survivors: paediatrics, developmental paediatrics, nutrition/dietary sciences, paediatric surgery, paediatric respirology and paediatric cardiology. Additional subspecialties or allied health professionals should be engaged as needed.	4	B-NR

CDH, congenital diaphragmatic hernia; NR, non-randomised.

Table 15 New recommendations regarding pain, analgesia and neuromuscular blockade management in CDH[143–147 149 150]

New recommendations	Strength of consensus	Level of evidence
15.1 All infants with CDH requiring mechanical ventilation should have personalised analgesic/sedation management that is guided by a clinically applicable and appropriately validated pain/sedation scoring tool.	4	B-NR
15.2 Intravenous opioid (morphine or fentanyl) should be administered as a CI in combination with a short-acting benzodiazepine, which may reduce opioid dosing requirements.	3	B-NR
15.3 Routine neuromuscular blockade should be avoided in preoperative stabilisation, but its use should be considered for infants with escalating severity of pulmonary hypertension or if ventilation targets are difficult to achieve.	4	C-LD
15.4 Postoperative use of intravenous acetaminophen should be considered as a means of reducing overall opioid requirements.	3	B-NR

CDH, congenital diaphragmatic hernia; CI, continuous infusion; LD, limited data; NR, non-randomised.

There is little evidence to address the role of neuromuscular relaxation in preoperative stabilisation of infants with CDH. A prospective cohort study of 15 mechanically ventilated infants with CDH demonstrated a significant decrease in compliance after the administration of pancuronium.[151] Furthermore, a multicentre registry review found that prolonged use of sedation and/or muscle relaxation was associated with longer lengths of stay and a higher mortality rate, which mirrors findings from the CHNC Database where the use of neuromuscular relaxation pre-repair occurred with nearly twice the frequency in non-survivors versus survivors (87% vs 48%).[146] These data appear to suggest that neuromuscular paralysis is added when patients with severe disease fail to stabilise.[146]

DISCUSSION AND CONCLUSION

In creating this update, the Canadian CDH Collaborative has sought to maintain its CPG as a 'living document' by updating and adding recommendations to care areas where new evidence has emerged. This updated CPG provides an evidence-based and consensus-driven management framework that aims to improve outcomes and encourage synthesis of new knowledge through targeted research and quality improvement efforts.

Author affiliations
[1]Department of Pediatric Surgery, Harvey E. Beardmore Division of Pediatric Surgery, Montreal Children's Hospital of the McGill University Health Centre, Montreal, Quebec, Canada
[2]Department of Surgery, BC Children's Hospital, University of British Columbia, Vancouver, British Columbia, Canada
[3]Department of Pediatric Surgery, Harvey E. Beardmore Division of Pediatric Surgery, Montreal Children's hospital of the McGill University Health Centre, Montreal, Quebec, Canada
[4]Division of Maternal and Fetal Medicine, Department of Obstetrics and Gynecology, Mount Sinai Hospital, University of Toronto, Toronto, Ontario, Canada
[5]Neonatology, Montreal Children's Hospital of the McGill University Health Centre, Montreal, Quebec, Canada
[6]Department of Surgery, Section of Pediatric Surgery, Alberta Children's Hospital, University of Calgary, Calgary, Alberta, Canada
[7]Department of Pediatrics and Child Health, Section of Neonatology, Max Rady College of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada
[8]Department of Pediatric Surgery, McMaster Children's Hospital, Hamilton, Ontario, Canada
[9]Department of Pediatrics, Division of Neonatology, Laval University, Quebec City, Quebec, Canada
[10]Department of Pediatric Surgery and Manitoba Institute of Child Health, University of Manitoba, Winnipeg, Manitoba, Canada
[11]Child Health Evaluative Sciences, Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada
[12]Department of Obstetrics & Gynaecology, Mount Sinai Hospital, Ontario Fetal Centre, Toronto, Ontario, Canada
[13]Department of Anesthesia, BC Children's Hospital, University of British Columbia, Vancouver, British Columbia, Canada
[14]Department of Surgery, Division of General and Thoracic Surgery, The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada
[15]Department of Surgery, Division of Pediatric General and Thoracic Surgery, The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada

X Pramod Puligandla @DrPuligandla, Elena Guadagno @GuadagnoElena and Gabriel Altit @CardioNeo

Collaborators The Canadian Congenital Diaphragmatic Hernia Collaborative.

Contributors A three-member steering committee (PP, ES, RB) was formed to oversee the CDH Collaborative's guideline development process, to finalise the guideline panel membership and contributors to the literature reviews, to critically appraise all materials generated during the evidence review process, oversee the final guidelines endorsement process and prepare the manuscript. PP acted as guarantor. They were specifically involved in the preparation of sections on haemodynamics (PP), ECLS (RB), non-primary surgical repair (ES), type of surgical repair (ES), repair on ECLS (ES/PP), and pain control and analgesia (ES). EG was the research director for the project who oversaw its design, the literature search and screening, as well as the editing of the final revised version of the manuscript and supplemental materials. AD was involved with the literature search and abstract screening, the critical appraisal and preparation of the section on surgery on ECLS, as well as the revision of the final submitted manuscript. OG was involved with the literature search and abstract screening, the critical appraisal and preparation of the section on haemodynamics, as well as the revision of the final submitted manuscript. NA was involved with the critical appraisal and preparation of the sections on prenatal diagnosis and fetal therapy, as well as revision of the final submitted manuscript. GA was involved with the literature search and abstract screening, the critical appraisal and preparation of the sections on echocardiography, role of PGE and target pulmonary vasodilator therapy, as well as the revision of the final submitted manuscript. MB was involved with the literature search and abstract screening, the critical appraisal and preparation of the section on surgical readiness, as well as the revision of the final submitted manuscript. SF was involved with the literature search and abstract screening, the critical appraisal and preparation of the section on type of surgical repair, as well as the revision of the final submitted manuscript. SD was involved with the literature search and abstract screening, the critical appraisal and preparation of the section on ventilation, as well as the revision of the final submitted manuscript. HF was involved with the critical appraisal and preparation of the section on gastro-oesophageal reflux as well as the revision of the final submitted manuscript. AH was involved with the literature search and abstract screening, the critical appraisal and preparation of the sections on echocardiography, role of PGE and target pulmonary vasodilator therapy, as well as the revision of the final submitted manuscript. RK was involved with the literature search and abstract screening, the critical appraisal and preparation of the section on ECLS as well as the revision of the final submitted manuscript. MO was involved in the concept and design of the work, as the facilitator for our Delphi consensus process, as well as the revision of the final submitted manuscript. DP was involved with the literature search and abstract screening, the critical appraisal and preparation of the section on role of ECLS, as well as the revision of the final submitted manuscript. GR was involved with the critical appraisal and preparation of the sections on prenatal diagnosis and fetal therapy, as well as the revision of the final submitted manuscript. MT was involved with the literature search and abstract screening, the critical appraisal and preparation of the section on ventilation, as well as the revision of the final submitted manuscript. AZ was involved with the literature search and abstract screening, the critical appraisal and preparation of the section on ECLS as well as the revision of the final submitted manuscript. PC was involved with the literature search and abstract screening, the critical appraisal and preparation of the section on long-term follow-up, as well as the revision of the final submitted manuscript.

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ORCID iDs
Pramod Puligandla http://orcid.org/0000-0003-2671-328X
Elena Guadagno http://orcid.org/0000-0002-4616-9990
Gabriel Altit http://orcid.org/0000-0001-5141-0964
Martin Offringa http://orcid.org/0000-0002-4402-5299
Dylan Patel http://orcid.org/0000-0002-4533-4595

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